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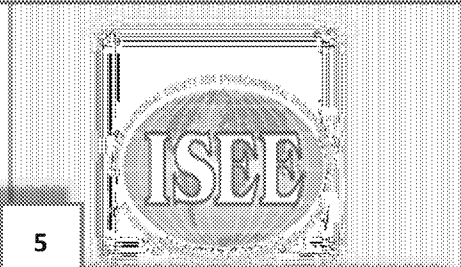
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Meet our researchers

Newsletter

Issue 4 | October 2016

EDITORIAL

Welcome to the October 2016 newsletter!

EXPOsOMICS has been very busy in the last quarter. The project participated in a series of conferences and workshops, such as *IARC's 50th Anniversary Conference* and the workshops held at *UKEMS 2016 (King's College London)*, *ISEE* and *ISES in Utrecht*.

A highlight is the recent publication of the "*The exposome in practice: Design of the EXPOsOMICS project*" article. In the article, the project and its goals are described, as well as the methods used to achieve them. One of the main project aims is to predict individual disease risk related to the environment, by characterizing the external and internal exposome for common exposures (air and drinking water contaminants) during critical periods of life, including in utero.

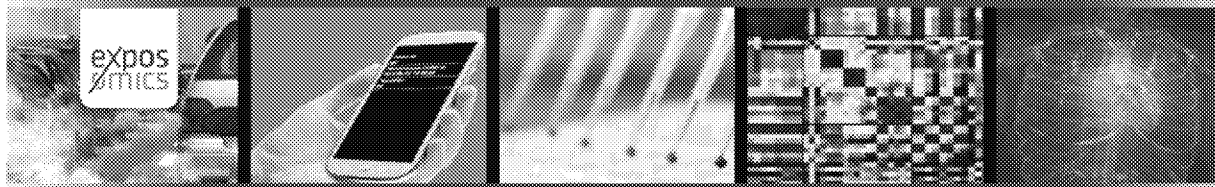
The newsletter has a few pages dedicated to our existing and new researchers. In this edition, they talk about their work and contributions to the project. There are very exciting times ahead as the project enters its final 6 months, having been granted the 6 months no-cost extension by the European Commission.

The EXPOsOMICS Annual Meeting will be hosted by Utrecht University this year, between the 27-28th October. Partners from various Working Groups within the project, alongside Work Package leaders and Principal Investigators will update on the project's state of advancements. Alongside this, the planning and preparations of the project Final Meeting are ongoing. This will be held next year, in early 2017, before the project will come to an end.

Finally, a massive thank you to all the contributors to this edition for their efforts and support!

Enjoy the newsletter!

Michaela Dijmarescu
Project Coordinator
EXPOsOMICS



The Exposome: moving from concept to practice *International Society of Exposure Science, Utrecht 2016*

by **Eduardo Seleiro (IARC)**
& **Dr. Jelle Vlaanderen (IRAS)**

The annual meeting of the International Society of Exposure Science (ISES) on the theme “Interdisciplinary approaches for health and the environment” took place in Utrecht, the Netherlands, from October 9-13, 2016.

The third day of the meeting included a whole day dedicated to the theme “The Exposome: From concept to practice”. The session was chaired by **Roel Vermeulen**, from **Utrecht University in the Netherlands**, and **David Balshaw** from the **National Institute of Environmental Health Services (NIEHS) in the USA**, and aimed to present and discuss the current status and future directions of research in this area.

The full program of the symposium is featured by following the link below:

<https://www.eiseverywhere.com/ehome/157736/434039/>

Christopher Wild, Director of the International Agency for Research on Cancer in Lyon, France and the person that originally coined the term “exposome”, provided the keynote address of the meeting. **Dr. Wild** gave an overview of the progress made since his original proposal of the exposome concept in 2005, how this new paradigm for exposure research has driven the development of a number of projects, how the concept itself is evolving as a result of the experience gained in this short time, and some of the challenges to be addressed in order to ensure research on the Exposome provides useful data to underpin policies for public health.

The prompt

The term “exposome” was coined by Dr. Wild when he realized that a focus on disease prevention rather than treatment is crucial to stop the projected increase in non-communicable disease (in both countries with a high and a low human development index) and spiraling costs of treatment. With the knowledge that the majority of disease has a lifestyle or environmental cause and the realization that for many common diseases etiology is still unknown there is a large potential for disease prevention.



October 9-13, 2016

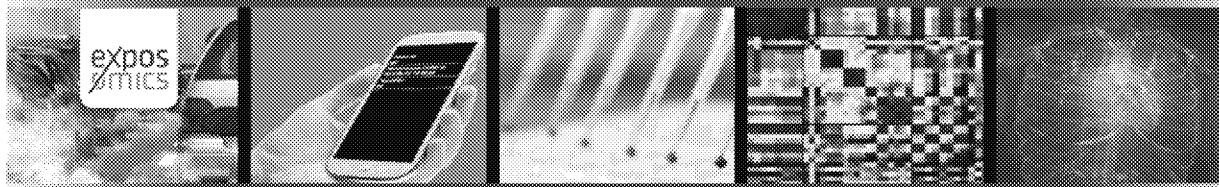
In 2005, Dr. Wild’s original call was to complement the large amount of knowledge on the genome (the result of significant funding over many years) with an exposome, focusing on the role of the environment in disease etiology.

The promise

The promise of the exposome is a paradigm shift to capture a far greater breadth of exposures for a given person including agnostic approaches, analysis of mixtures, and considering timing of exposure. Dr. Wild distinguishes between three different exposome domains: general external (for example socio-economic factors), specific external (for example air pollution), and internal exposure (for example urinary biomarkers). Ideally we would like to track these different domains over an individual’s lifetime. Naturally there will be many challenges for the implementation of the exposome concept in research including its scale and complexity, its dynamic, technical assessment, and data analysis. However it is important to realize that partial characterization can take us forward significantly.

Dr. Wild remarked that is not correct to think of the exposome to mirror the genome: the exposome in its entirety is unlikely to be characterized, therefore individual level application is unlikely for the exposome and its impact is to be expected more on population level for public health. Potential contributions include establishing causes (hazard and risk), exposure assessment, dose response analysis, providing biological plausibility, evaluating interventions, stratifying risks, and surveillance of exposures.





The Exposome: moving from concept to practice *International Society of Exposure Science, Utrecht 2016*

With all the new technologies available (questionnaires, GIS based modeling, mobile devices, biomarkers in different tissues, omics) to assess the exposome, it is important to keep the research questions in mind.

Furthermore, we should optimize the interaction between population research (causes and prevention), basic science (molecular alterations), and the patient (personalized treatment).

The practice

Even though the field of exposome research is new there are already a number of successful applications of assessing the (partial) exposome including environment wide association studies (for example using the NHANES data) and the analysis of the public health exposome in relation to preterm birth rates. Several projects within IARC have also generated useful insights into the exposome. The application of metabolomics in studies of diet has yielded several useful predictors of (specific) food intake. This information is now collected in the Exposome-Explorer which contains so far data on 489 dietary and pollutant biomarkers. The second example is from a study in which variation in genomic landscape of clear cell renal cell carcinoma across Europe was linked to exposure to aristolochic acid (quantified via DNA adducts). This example demonstrates how in vitro data can be linked to human cancer data to explore the exposome. The third example focused on early life exposure and mechanistic precursors of childhood cancer. In this study the impact of sustained smoking and exposure to aflatoxin during pregnancy on the methylome in early childhood was shown.

The perspective

Dr. Wild closed his presentation with a personal perspective on what needs to be addressed in the years to come. Issues include validation of exposure measurements, data integration and analysis and matching OMICS techniques with biology.

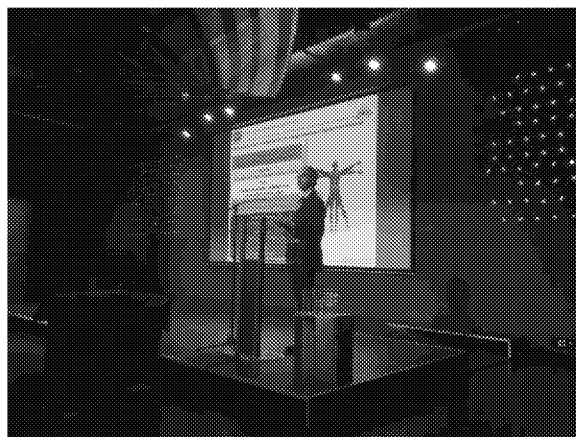
Importantly, we need to remain focused on the question that spurred the introduction of the exposome concept: "characterizing exposure-disease relationships". Because exposome research is still in its infancy we need to apply 'taste and see' approaches to see what problems we face and most importantly we need continued funding, including investments in methods development.



Dr. Wild (IARC), Keynote address at ISES

Dr. Wild closed his presentation with a quote from Winston Churchill: "Don't argue the matter. The difficulties will argue for themselves".

The session continued with presentations on early results from some of the largest projects on the Exposome from the USA, Japan and Europe. The afternoon sessions focussed on proof-of-principle studies on practical applications of exposome methodologies, and examples of the application of statistical and causal inference in Exposome studies.



Dr. Balshaw (NIEHS), CHEAR program

The morning sessions were webcast live and a recording can be viewed on <http://ises2016.org/live-webcast/>





IARC's 50th Anniversary & EXPOsOMICS Lyon, France, June 2016

by Eduardo Seleiro(IARC)

The *International Agency for Research on Cancer (IARC)*

organised a major international conference to celebrate its 50th anniversary. Under the theme "**Global Cancer: Occurrence, Causes, and Avenues to Prevention**",

the conference took place from 7–10 June 2016 in **Lyon, France**, and involved the participation of nearly 1000 scientists from more than 80 different countries from across the world.



The major themes of the conference were structured around the three core areas of activity of IARC, featuring keynote lectures from a panel of leading international cancer researchers, as well as a number of smaller themed workshops and symposia. The programme also included debates on controversial issues together with "big picture" lectures on cancer, science, and society.

The conference celebrated IARC's unique contribution to the state of knowledge on cancer prevention, and offered an opportunity to discuss key priorities and opportunities for future research.

One of the topics featured the major emerging research of the Exposome, which was the subject of a parallel session, on "Systems perspectives of the exposome" co-chaired by Jiri Zavadil (IARC) and Paolo Vineis (Imperial College London, UK). Paolo Vineis gave the introductory lecture in which he highlighted the revolution introduced by new external and internal exposome techniques in epidemiology (including omics) that allow etiologic research to make a leap forward. This was followed by presentations from Roel Vermeulen (Utrecht University, the Netherlands) Silvia Balbo (University of Minnesota, USA) and Ludmil Alexandrov (Los Alamos National Laboratory, USA) focussing on different aspects of Exposome research. Finally, results from some of the largest studies on the Exposome were presented in a number of posters by participants working in these projects.

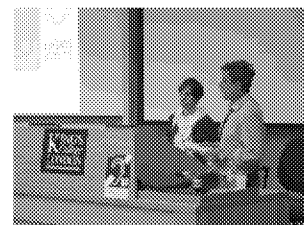
The focus on the Exposome reflected one of the major features of the IARC's work over the last five decades, namely the advantages of taking an interdisciplinary approach to research, drawing on expertise in epidemiology, laboratory sciences, biostatistics and bioinformatics.

EXPOsOMICS @UKEMS Conference King's College London, June 2016

by Prof. David Phillips (KCL)
Dr. George Preston (KCL)

Between 26 -29th June
King's College London
held the 39th Annual
Meeting of the
UK Environmental
Mutagen Society.

UKEMS is an annual scientific meeting where national and international researchers gather to present their work.



The meeting had "around 150 registered participants and it featured a number of symposia, including, on the final day, one on **EXPOsOMICS**", according to David Phillips, Professor of Environmental Carcinogenesis at King's College London, and Partner to the EXPOsOMICS project.

The UKEMS session on **EXPOsOMICS** held on the 29th June was co-chaired by Prof. Vineis and featured seven presentations from members of EXPOsOMICS which discussed their latest findings. Prof. Jos Kleinjans (Maastricht University) gave a Keynote lecture on 'Transcriptomics responses amongst environmentally exposed study population' and Prof. Nicole Probst-Hensch (University of Basel, Swiss Tropical and Public Health Institute) on 'Challenges in investigating the asthma exposome'.

Presentations were also done by Dr. Cristina Villanueva (ISGlobal) on 'Exposure to disinfection by-products in swimming pools and associated early effect biomarkers', Prof. Augustin Scalbert (IARC) presented on 'Metabolomics and the exposome in epidemiology' and Dr. John Gulliver (ICL) on 'Air pollution measurements and modelling to characterise the external exposome'.

Dr. George Preston (KCL), presented his findings on 'Probing the internal exposome using untargeted albumin adductomics'. "Giving a presentation was a great opportunity to share recent results with the multidisciplinary community of UKEMS" said Dr. Preston, adding that he was able "to describe the methods we have developed for protein adductomics, and to highlight collaborative work done with colleagues at the University of California, Berkeley".

More details on the UKEMS 2016 meeting at
<http://www.ukems2016.org/>



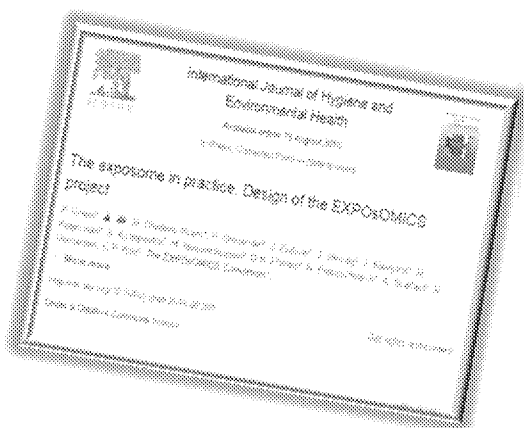


EXPOsOMICS Descriptive Paper

“The exposome in practice: Design of the EXPOsOMICS project” was published in August 2016 in the *International Journal of Hygiene and Environmental Health*. The main aim was to explain the study design and methodologies used to assess the internal and external exposome.

The paper looks at the following:

- (1) Personal exposure assessment within existing European population studies, exploiting available tools and methods developed for personal exposure monitoring (PEM);
- (2) Multiple “omic” technologies for the analysis of biological samples.



It highlights the novelty of the relationship between external exposures and global profiles of molecular features in the same individuals, towards the development of “next generation exposure assessment” for environmental chemicals and their mixtures. See the full paper at

<http://dx.doi.org/10.1016/j.ijheh.2016.08.001>

International Society of Environmental Epidemiology update Dr. Roel Vermeulen

The annual meeting of the International Society of Environmental Epidemiology (ISEE) on the theme “Old and new risks: challenges for environmental epidemiology” took place in Rome, Italy, from September 1-4, 2016.

Roel Vermeulen, Ass. Professor of Molecular Epidemiology and Exposure Science at Utrecht University, and Partner to the EXPOsOMICS project gave a keynote address on the use of OMICs technologies in environmental epidemiology. Dr. Vermeulen addressed the question of whether OMIC-technologies can help in elucidating the unattributable proportion of the modifiable part of the global burden of disease. He introduced the concept of the exposome and indicated how the field of exposomics fits in the molecular epidemiology paradigm. He showed evidence of several proof-of-principle studies using OMICs technologies such as metabolomics, epigenetics and transcriptomics in which successfully direct measures of exposure were obtained, exposure-specific or broader biological imprints, that could be related to biological effects and/or disease. Although it is still early days these proof-of-principle studies show the potential strength and applications of the exposome paradigm in public health.



Dr. Vermeulen (IRAS), Keynote address at ISEE

On the Sunday after the ISEE conference a half-day workshop was organised by David Balshaw (NIEHS), Roel Vermeulen (IRAS) and Paolo Vineis (ICL). The workshop focussed on the exposome from concept to practice and featured the HELIX, EXPOsOMICS, JECS, Hercules and CHEAR research programs. The workshop highlighted the practical problems of implementing the exposome concept in epidemiological research and the statistical and causal interpretation challenges brought by high dimensional data. The workshop was ended with a presentation of Dr. Linda Birnbaum (Director NIEHS) who talked about translation of exposome research into risk assessment and policy.

A recording can be viewed on:

<http://www.isee2016roma.org/conference-videos/>



EXPOSOMICS Research Updates

Dr. Sonia Dagnino (ICL)
Adductomics analyses

Sonia Dagnino recently joined ICL, working on a project called EXACT - **"Identifying biomarkers of Exposure leading to Lung Cancer with AdduCTomics"**.

Adductomics is a technique that has been developed by Professor Rappaport's team at UC Berkeley that allows the measure of human serum albumin adducts in serum.

In the context of EXPOSOMICS, the method has been imported and adapted by Professor Phillips' team at King's College London. The aim of **EXACT is to apply adductomics to the understanding of lung cancer aetiology**. Adductomic analysis will be performed on a subset of the EPIC cohort. Adduct profiles for cases and controls will be paired with air pollution estimates, smoking status and epigenetic measurements. After identification, these adducts could be used as markers of exposure and also indicate which compounds may be responsible for carcinogenesis.

Recently, Professor Rappaport's team at UC Berkeley has updated and improved the methodology which is now based on high-resolution MS, that not only increases the number of measured adducts (> 100 adducts), but also allows their structural identification.

In EXPOSOMICS, Sonia Dagnino will be involved in statistical analysis of adductomics data and annotations for metabolomics data.

Dr. Akram Ghantous (IARC)
Epigenetics in EXPOSOMICS

Genome-wide DNA methylation was evaluated in five studies within EXPOSOMICS, spanning all ages of human life. The analysed biospecimen constituted of cord and peripheral blood, totalling 2,304 samples analysed by Illumina HM450 arrays, and the data was generated by the Epigenetics Group at the International Agency of Research on Cancer (Lyon, France), with cost-effective procedures and a sample success rate of 99.9%.

In May 2016, the DNA methylome data was completed for all EXPOSOMICS studies, assessed for quality, and transferred to all EXPOSOMICS partners. Ongoing data analysis has shown that the data quality is high and reproducible allowing the analysis to proceed without major batch-effect corrections. Recent results have identified epigenetic signatures of birth weight and epigenetic predictors of gestational age (*manuscripts in preparation*).

Dr. Pooja Jain (ICL)
Investigating the effects of mixtures

Dr. Pooja Jain is a post-doctoral research associate (Computational Biology/Bioinformatics) at the Department of Surgery and Cancer, Imperial College London. She is currently collaborating with the MRC-PHE Centre for Environment and Health (Medical Research Council – Public Health England) to extend her expertise in data analyses, machine learning and biostatistics within the EXPOSOMICS project.

Dr. Jain has been researching the possibility of using multi-variate sparse Partial Least Squares (sPLS) models to study the effect of mixtures and to propose a method for cross-omics. sPLS is an exploratory statistical approach with specific focus on variable selection through data integration. The selected response variables are proposed as highly associated to the predictor(s) and thus deemed suitable for specific hypotheses generation and bio/statistical inferences.

Currently, Dr. Jain is looking into the proteomics and metabolomics datasets from PISCINA II study. The method, which is near to completion, will then be tested in different sub-projects/cohort/studies to achieve the goals of WG10 (cross-omics) data analyses.

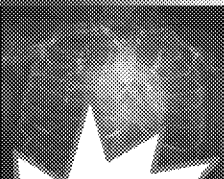
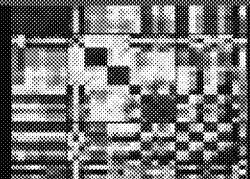
Dr. Jain has also been involved with providing the bioinformatics and statistical support to the Children Studies Working Group. She analysed data, specifically on the association of maternal methylation changes and gestational age, within the PACE-EXPOSOMICS framework.

Moreover, the IARC Epigenetics Group has initiated collaborations between EXPOSOMICS and other large consortia, namely the International Childhood Cancer Cohort Consortium and the Pregnancy and Childhood Epigenetics Consortium, allowing greater statistical power as well as the ability to analyze rare exposures or phenotypes and to compare associations across several countries and continents.

These collaborations as well as ongoing 'cross-omics' analysis between epigenomics and other – omics data available within these consortia hold further promise to our ability to move the Exposome concept from theory to practice.

For more details on the research work done in EXPOSOMICS, please visit <http://www.exposomicsproject.eu/>





IN THE
SPOTLIGHT

Dr. Oliver Robinson (ICL)

on joining the project and working on Children Studies



Oliver Robinson has joined EXPOSOMICS as an MRC-PHE Centre Research Fellow. Previously, Oliver worked as the Scientific Coordinator for HELIX, based at IS Global in Barcelona, Spain. HELIX is the 'sister' project of Exposomics, focussing on the exposome during early stages of life. During his time working for HELIX, Oliver looked after some of the birth cohorts such as Rhea in Greece and INMA in Spain, which contribute data to both projects.

Welcome to the project, Oliver. Tell us about the work you do in EXPOSOMICS. I brought my experience of child development studies to the Children's study component of EXPOSOMICS. Specifically, I have been analysing molecular profiles of stored cord blood samples in relation to both air pollution and birth weight. Birth weight is an interesting health trait to study since it reflects the general health of both the mother and developing foetus during pregnancy and is an important predictor of the health of the child through their life.

Can you share with us a highlight of your work so far?

We have identified a number of molecular features associated with both an increase and decrease in birth weight. Some of these features are correlated suggesting common molecular origins or common biological pathways. Despite appearing to be important for foetal growth the identity of these compounds is still unknown. We are currently working with our colleagues at IARC to identify these features, with further experiments if necessary.

Do you have any papers planned, based on your findings so far?

I think the initial paper to come out of my work will be related to the link between the metabolome (i.e. the set of small molecules detectable in cord blood) and birth weight. The impact of air pollution on the metabolome will also be explored.

This all sounds very interesting. Can you tell us more about your future plans in EXPOSOMICS?

Further down the line I plan to examine the links between molecular markers at different levels of biological organisation such as proteins and DNA, and how these richer biological networks impact on foetal growth.

Dr. Pekka Keski-Rahkonen (IARC)

Metabolomics – an emerging technique in exposome research

Several complementary state-of-the art analytical techniques were employed in the EXPOSOMICS project to analyze the transcriptome, epigenome and metabolome in blood samples from cohorts exposed to air pollution or disinfection by-products. The analysis of metabolome was performed at the International Agency for Research in Cancer (IARC) in Lyon, France using untargeted metabolomics.

Metabolomics is an emerging technique in exposome research that enables monitoring relative concentrations of up to several thousand metabolites from each sample, for which associations with exposures or other variables can be calculated.

The process begins with the analysis of samples by mass spectrometry and is followed by data preprocessing and statistical analysis to find the discriminating metabolites, such as those having plasma concentrations associated with swimming

In a chlorinated pool in the Piscina study, which may reflect exposure to disinfection by-products.

At IARC, all metabolomics analyses were completed in May 2016. This included extraction and analysis of more than 2,900 serum and plasma samples, which took approximately 650 hours of continuous analysis by a high-resolution mass spectrometer, resulting in almost 1TB of data. Preprocessing of the data was completed by the end of May, and several EXPOSOMICS collaborators have already finished the statistical analysis.

The subsequent identification of the discriminants is ongoing at IARC by Dr. Agneta Kiss, Ms. Nivonirina Robinot, and Dr. Pekka Keski-Rahkonen. Two projects, Piscina and the Children Study, are close to completion and the results will be submitted soon for publication.



EXPOsOMICS & Other Conferences

Human BioMonitoring Conference April 2016

The **2nd International Conference on Human BioMonitoring** was held in Berlin, Germany, between April 17-19, 2016.

Paolo Vineis presented 'The role of the "omics-techniques" in HBM, current and future applications'.

ISEE 28th Annual Conference – Exposome Workshop September 2016

The **International Society for Environmental Epidemiology (ISEE)**, 28th Annual Conference took place in Rome between 1-4 September 2016. A half day workshop was organised on Sunday, 4th September, by David Balshaw (NIEHS), Roel Vermeulen (IRAS) and Paolo Vineis (ICL).

Latest publications

Font-Ribeira, L., et al (2016), *Environmental and personal determinants of the uptake of disinfection by-products during swimming*, Environ Res. 2016 Aug; 149:206-15.

Doi: 10.1016/j.envres.2016.05.013. Epub 2016 May 20.

Vineis, P., et al (2016), *The exposome in practice: Design of the EXPOsOMICS project*, Int J Hyg Environ Health. 2016 Aug 19. pii: S1438-4639(16)30130-4.

Doi: 10.1016/j.ijheh.2016.08.001. [Epub ahead of print]

Agier, L. et al (2016), *A Systematic Comparison of Linear Regression – Based Statistical Methods to Assess Exposome-Health Associations*, Environ Health Perspectives. 2016 May; Doi: 10.1289/EHP172

Morley, D. et al. (2016), *Methods to improve traffic flow and noise exposure estimation on minor roads*, Environ Pollut. 2016 Jun;

Doi: 10.1016/j.envpol.2016.06.042

Quick news...

EXPOsOMICS Annual Meeting 2016

The meeting will take place over 27-28th October in Utrecht, at the Utrecht University Campus.

In the afternoon of the second day, Utrecht University will also host an Exposome Symposium for all interested participants.



Project Extension

The project's six month no-cost extension has been formally approved by the European Commission and the project's end date is now Apr 30th, 2017.

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